REVIEW

The role of the Tei index in assessing for cardiotoxicity from anthracycline chemotherapy: a systematic review

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Abstract

Background: Anthracycline agents are known to be effective in treating tumors and hematological malignancies. Although these agents improve survival, their use is associated with cardiotoxic effects, which most commonly manifests as left ventricular systolic dysfunction (LVSD). As such, guidelines recommend the periodic assessment of left ventricular ejection fraction (LVEF). However, as diastolic dysfunction likely proceeds systolic impairment in this setting, the role of Tei index may offer additional benefit in detecting subclinical LVSD.

Methods: We conducted a systematic review to investigate the evidence for the use of Tei index in assessing subclinical cardiotoxicity in patients receiving anticancer agents. A search of Medline and EMBASE was performed and relevant studies were reviewed and narratively synthesized.

Results: A total of 13 studies were included with a total of 800 patients (mean age range 46–62 years, percentage of male participants ranged from 0–86.9%). An increase in Tei index was observed in 11 studies, which suggested a decline in cardiac function following chemotherapy. Out of these, six studies indicated that the Tei index is a useful parameter in predicting cardiotoxic LVSD. Furthermore, five studies indicated Tei index to be superior to LVEF in detecting subclinical cardiotoxicity.

Conclusions: Though there are some studies that suggest that Tei index may be a useful indicator in assessing subclinical anthracycline-related cardiotoxicity, the findings are inconsistent and so more studies are needed before the evaluation of Tei index is performed routinely in patients receiving chemotherapy.

Key Words

- myocardial performance index
- Tei index
- cardiotoxicity
- 2D echocardiography

Introduction

Anthracycline agents are known to be effective in treating solid tumors and hematological malignancies (1). They are commonly used in clinical practice with reported usage rates of 32% of breast cancer patients (2) and 57–70% of elderly lymphoma patients in other studies (3, 4). Although these treatments have led to

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improved survival rates in cancer patients, their side effects are known to increase morbidity and mortality either via cardiotoxicity or the accelerated development of cardiovascular disease (5). Cardiotoxicity ultimately impacts myocardial structure and function which can manifest as cardiac arrhythmias, myo-pericarditis or stress cardiomyopathiesn (5). The most common anthracycline cardiotoxic side effect includes left ventricular systolic dysfunction (LVSD) which is thought to affect approximately one-third of all patients exposed to chemotherapy treatments (6). Subclinical cardiotoxicity is a major cause of concern because it may justify switching to alternative or discontinuing cancer treatments to minimize long-term damage to the myocardium (7).

Transthoracic echocardiography (TTE) allows for repeated and standardized assessments of the myocardium and is the imaging modality of choice for chemotherapy patients due to its wide availability, low cost and relatively high reproducibility (8). International guidelines provide robust assessment criteria for assessing subclinical cardiotoxicity which includes a heavy reliance on 2D left ventricular ejection fraction (LVEF) along with the more recent inclusion of global longitudinal strain (GLS) and 3D-LVEF (7). At present, subclinical cardiotoxicity is defined by (1) >10% points decrease to a value below the lower limits of normal of LVEF or (2) >15% relative percentage reduction from baseline GLS (7). However, a reduction in LVEF is a relatively late expression of LVSD (9). Furthermore, LVEF is affected by inter-observer variability, reliance on optimal 2D images and geometric assumptions (10). In addition, subclinical cardiotoxicity is thought to begin with changes in left ventricular diastolic function with subsequent progression onto LVSD (11). Therefore, an assessment tool such as Tei index may enable subclinical cardiotoxicity to be detected prior to a deterioration in LVEF. Tei index is advantageous as it incorporates both systolic and diastolic timing intervals (13, 14). Tei index is a numeric value derived from the sum of isovolumetric contraction and isovolumetric relaxation divided by total ejection time (Fig. 1) which can be calculated for both left and right ventricular myocardial performance (13, 14). It is advantageous as it can be assessed by Pulse Wave Doppler and Tissue Doppler echocardiography (Fig. 2). Furthermore, several studies have indicated that Tei index is independent of heart rate (although several measurements are advised with irregular heart rhythms), preload and afterload (12) making Tei index an easy parameter to assess overall myocardial performance which is accepted in many clinical settings.

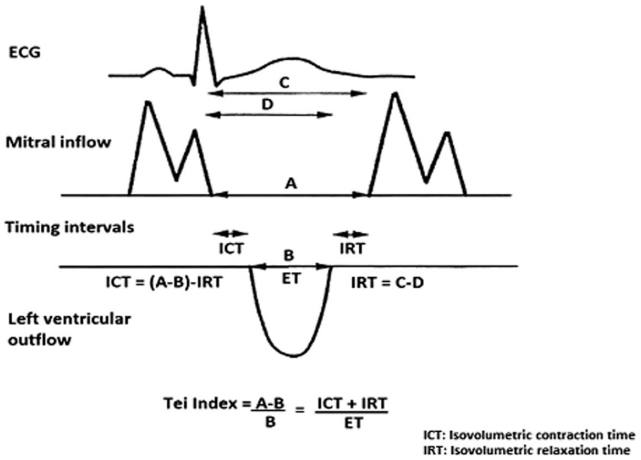

Figure 1
Schematic representation of Tei index.

The role of Tei index in the detection of subclinical cardiotoxicity is currently controversial, with studies both in support (14, 15) and against (16) its use. To better understand the role of Tei index in the detection of

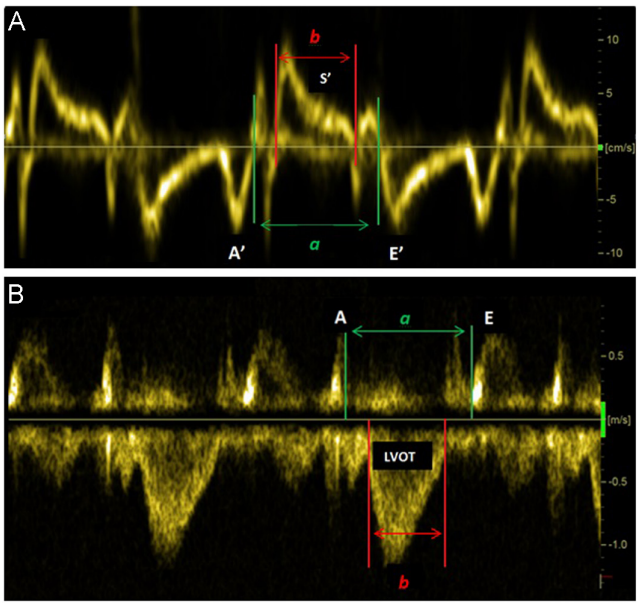

Figure 2
Tei index using Pulse Wave Doppler and Tissue Doppler echocardiography. (A) Tissue Doppler imaging of the septal mitral valve annulus in the apical 4 chamber. A is measured between the end of late diastolic myocardial velocity (A′) to the onset of early diastolic myocardial velocity E′. B is the time interval of the entire systolic myocardial velocity (S′). All intervals measured outer edge to outer edge of the respective defections. (B) Pulse wave Doppler imaging at the midpoint between the left ventricular outflow tract and mitral valve in a modified apical 4/5 chamber view. *a* is measured from the termination of the mitral inflow active filling wave (A) to the onset of early mitral inflow (E). *b* is measured from the initial to termination deflection of left ventricular outflow tract (LVOT). All intervals measured outer edge to outer edge of the respective defections.

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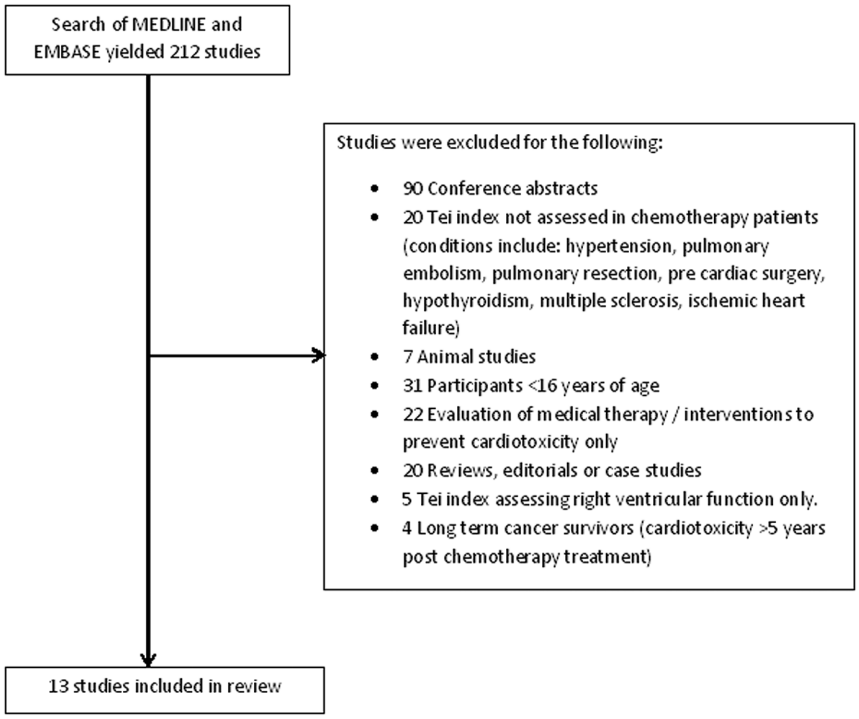

Figure 3
Flow diagram of study selection.

subclinical cardiotoxicity in patients who have received anthracycline chemotherapy, we conducted a systematic review of the literature.

Methods

We conducted a systematic review to evaluate the role of Tei index in assessing for subclinical LVSD cardiotoxicity in patients receiving anticancer agents. Inclusion criteria included: ≥16 years of age, use of anthracycline or derivatives as part of the patient's treatment regimen and left ventricular systolic function at baseline and follow-up. Exclusion criteria included: conference abstracts, review articles, editorial pieces, cases studies, animal studies, cardiotoxicity not assessed in cancer patients, studies assessing right ventricular Tei index only, assessment of interventions in the prevention of cardiotoxicity, cardiotoxicity occurring >5 years post-therapy and studies which also included radiotherapy as part of the patient's treatment. Tei index was defined as depicted in Fig. 1. Studies assessing Tei index by Pulsed wave Doppler imaging or Tissue Doppler imaging were included as sensitivity of both methods are comparable (9).

A search of MEDLINE and EMBASE was undertaken on OVID using the search terms 'Tei index' 'myocardial performance' 'cancer' 'leukemia' 'leukaemia' 'lymphoma' 'chemotherapy' 'cardiotoxicity' and 'anthracyclines' in November 2020. The subsequent results were independently reviewed for inclusion by two reviewers (S B and C S K). Full text of potentially relevant studies were obtained and reviewed prior to final inclusion. Data extraction was performed by two independent reviewers (S B and C S K). For each study the following was extracted: study design, year, country of study performed, number of participants, mean age of participants, percentage of male participants, definition of cardiotoxicity, chemotherapy type and Tei index findings. All included studies were evaluated in accordance with the Newcastle Ottawa scale. The results of the extractions are presented in table with results narratively synthesized also.

Results

Our search yielded 212 potentially relevant studies. After a detailed review of titles, abstracts, and subsequently full articles for potentially relevant studies, 13 studies (1, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 30) were identified and included in the final review (Fig. 3).

The description of the studies and the patient characteristics are shown in Table 1. A total of 800 patients from ten prospective and three retrospective cohort studies were included. The number of participants in each study ranged from 23 to 100 with a mean age range of 46.1 to 61.1 years. Male gender distribution varied from 0 to 86.9%.

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Table 1 Study description and patient characteristics. Most pertinent data highlighted in bold italics.

Study ID Reference	Study design; year of study or publication; country	Proportion of cancers types	No. of participants	Mean age	% male	Chemotherapy agent; dose	Exclusion criteria
Ayhan 2012 (14)	*Prospective cohort study, published in 2012, Turkey*	***Breast cancer (73%), non-Hodgkins lymphoma (11%), Hodgkins lymphoma (9%), leiomyosarcoma (7%)***	***45***	***50.1***	***17.8%***	***Doxorubicin, average dose 268 mg/m²***	History of coronary artery disease, systemic hypertension, prior use of anthracycline therapy, chronic renal failure, chronic obstructive lung disease, non-sinus rhythm, abnormal LV systolic function, poor quality echo images and moderate to severe valvular heart disease
Belham 2007 (15)	*Prospective cohort study, published in 2007, United Kingdom*	***Hematological or solid tumor, not specified which***	***61***	***50***	***86.9%***	***Doxorubicin, average dose 293 mg/m²***	Withdrawn consent, pre-existing cardiac disease, cardiomyopathy, atrial fibrillation and died
DiLisi 2011 (17)	Prospective cohort study, published in 2011, Italy	***Breast cancer only***	***72***	***57***	***0%***	***Trastuzumab, Epirubicin, Flurouracil, Cyclophosphamide, Taxotere, Taxolo, doses unclear***	Abnormal LV systolic function and important pathologies (not specified but cohort included diabetes, hypertension, obesity, dyslipidemia and smokers)
Dodos 2008 (1)	Prospective cohort study, published in 2007, Germany	***Non-Hodgkin lymphoma (37%), breast cancer (29%), Hodgkin lymphoma (13%), acute myeloic leukemia (9%), multiple myeloma (3%), acute lymphatic leukemia (2%), lung cancer (2%), sarcoma (1%), chronic lymphatic leukemia (1%), malignant histocytoma (1%), other (2%)***	***100***	***46.1***	***48%***	***Doxorubicin, epirubicin, daunorubicin, mitoxantrone and idarubicin; mean cumulative anthracycline dose 226.1 mg/mL²***	History of cardiovascular disease, prior use of anthracycline therapy, chronic renal insufficiency, liver disease, uncontrolled systemic hypertension, left ventricular ejection fraction < 55%, patients with an age > 70 years and < 18 years
Dogru 2013 (18)	Prospective cohort study, published in 2013, Turkey	***Breast cancer (70%), lymphoma (30%)***	***50***	***46.6***	***16%***	***Fluorouracil, Cyclophosphamide, Doxorubicin, Cyclophosphamide, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine, Vincristine; mean anthracycline dose 222 mg/m²***	History of cardiotoxicity drug use, radiotherapy to the thoracic region, congestive heart failure, myocardial infarct during the previous year, prosthetic heart valve, moderate to severe valve disease, arrhythmia disorder, other cardiotoxic drug use and a history of severe chronic disease
Elalouani 2012 (19)	Prospective cohort study, 2008 to 2009, Morocco	***Breast cancer (84%) and other cancers (16%)***	***90***	***47***	***9%***	***Doxorubicin and Epirubicin, average dose: 356 mg/m² and 552 mg/m², respectively***	Poor echogenicity, incomplete echocardiographic follow-up or inconsistent echo measurements for two operators for the same patient

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Elbl 2006 (20)	Prospective cohort study, 2001 to 2013, Czech Republic	***Lymphoma only***	***47***	***49***	***57%***	***Cyclophosphamide, Doxorubicin; cumulative of doxorubicin 300 mg/m²***	None stated
Erdogan 2011 (21)	Prospective cohort study, 2009, Turkey	***Breast cancer (59%), lymphoma (28.2%), other (12.8%)***	***54***	***53.7***	***23.1%***	***Anthracyclines; total anthracycline dose 448.3 mL/m²***	History of systemic disease including diabetes, hypo/hyperthyroidism, hypertension, hemolytic, hepatic, renal diseases, coronary artery disease, congestive heart failure symptoms, LVEF < 50%, established structural heart disease such as cardiomyopathy, moderate or severe mitral or aortic valve disease; history of chemotherapy or radiotherapy, and planned radiotherapy, ST-segment or T-wave changes specific for myocardial ischemia, Q waves, and incidental left bundle branch block on electrocardiography
Mizia-Stec 2013 (22)	Prospective cohort study, published 2013, Poland	***Breast cancer only***	***35***	***Range 35–68***	***0%***	***Epirubicin: mean dose 414 mg/m² Doxorubicin: mean dose 278 mg/m²***	Clinical or echocardiographic (ejection fraction < 50%) evidence of heart failure, symptoms of acute cardiotoxicity during chemotherapy, severe or uncontrolled arterial hypertension, diabetes, coronary artery disease, left-side chest wall radiation in the patient's medical history, active smoking, abnormalities in the ECG (e.g. abnormal rhythm, bundle branch blocks), autoimmune or endocrine diseases and infections
Rohde 2007 (16)	Prospective cohort study, 2000 to 2002, Brazil	Breast cancer (80%), lymphoma (18%), other (2%)	55	49	9%	Fluoracil, Adriamycin, Cyclophosphamide, Adriamycin, and Vincristine; mean Adriamycin dose 304 mg/m²	None stated
Senju 2007 (23)	Retrospective cohort study, 1998 to 2000, Japan	Acute myeloid leukemia (52%), adult T cell leukemia (22%), lymphoma (26%)	23	47.2	52%	Doxorubicin total dose 420 mg/m²	Asynergy or significant valvular disease on echocardiography
Shaikh 2016 (24)	Retrospective cohort study, 2009 to 2013, The United States	Acute myeloid leukemia	86	62.1	55%	Mitoxantrone and cytarabine; average mitoxantrone dosage 144 mg	Recurrence of acute myeloblastic leukemia, history of stem-cell transplantation, pregnancy, age <18 years and history of heart failure or coronary artery disease
Zhang 2017 (30)	***Retrospective cohort study, 2013 to 2015, China***	***Large B-cell lymphoma***	***82***	***Range 24–72***	***50%***	***Cyclophosphamide (750 mg/m²), Epirubicin (50 mg/m² on day one), Vincristine (1.4 mg/m² to maximum dose of 2 mg/m²)***	***Pre-existing cardiac, renal or hepatic dysfunction, diabetes or hyperthyroidism; mass infiltration of the pericardium, myocardium or valves identified by echocardiography or radionuclide imaging***

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The studies included a variety of chemotherapy protocols as shown in Table 1. Breast cancer was the most common cancer type included in the studies, however, a variety of other cancers were also included (Table 1). Table 2 shows the quality assessment of the included studies using the Newcastle Ottawa scale. In general, all studies had patients with cancer receiving chemotherapy and measures were taken to ensure that LVSD was not present at the start. However, all the studies did not report adjusted outcomes so no stars could be assigned for comparability. Five of the included studies had reliable elements in the outcome domain for outcome ascertainment, follow-up and low degree of missing data but another five studies did not report outcomes. Clinical outcomes were clearly defined in seven of the included studies (1, 15, 19, 20, 21, 24, 30). Although there was a considerable variation in the criteria used to define the presence of cardiotoxicity all seven studies incorporated a reduction in baseline LVEF by ≥10% with and/or without the presence of symptoms.

The Tei index results for the included studies are shown in Table 3 with the most pertinent data highlighted in bold italics. Eleven studies showed an increase in Tei index values between baseline and follow-up with increased Tei index values at follow-up ranging from 0.41 ± 0.12 (15) to 0.66 ± 0.18 (24). Six of these studies (14, 15, 19, 21, 22, 30) indicated that a significant increase in Tei index at follow-up was a sensitive marker in the prediction of subclinical LVSD, in these studies Tei index at follow-up ranged from 0.41 ± 0.08 to 0.61 ± 0.10. Furthermore, when compared to LVEF, Tei index was superior in predicting subclinical cardiotoxic events with five studies (14, 15, 21, 22, 30) reporting an increased Tei index in the presence of a normal LVEF. Only three studies concluded Tei index not to be useful in predicting cardiotoxicity and that LVEF remained superior (16, 23, 24).

Only two of the 13 included studies reported Tei index in the relation to patients who went onto develop cardiotoxicity compared to those who did not (21, 24). Shaikh *et al.* reported no significant difference in Tei index at baseline in either of these groups (0.59 ± 0.14 vs 0.55 ± 0.17, $P=0.31$). However, at follow-up, Tei index was significantly higher in the cardiotoxicity group compared to the non-cardiotoxicity group (0.66 ± 0.18 vs 0.59 ± 0.17, $P=0.03$) (25). Erdogan *et al.* reported that Tei index in cardiotoxicity group was significantly higher than in the non-cardiotoxicity group (0.47 ± 0.07 vs 0.41 ± 0.08, $P=<0.05$. OR: 3.24, 95% CI 1.40–4.1, $P=0.02$) (22).

Discussion

This first systematic review of Tei index in the evaluation of subclinical cardiotoxicity has several key findings. First, patients who received chemotherapy appear to have increased Tei index post chemotherapy which suggests that chemotherapy is associated with a reduction in cardiac function. Secondly, only five studies have attempted to correlate Tei index with LVEF and it remains unclear if Tei index is equivalent, better or worse in identifying subclinical cardiotoxic LVSD. Thirdly, most of the studies to date are small and underpowered to evaluate cardiotoxicity. These findings suggest that there is the need for future larger studies to incorporate Tei index for the evaluation of subclinical cardiotoxic LVSD and whether Tei index is a tool fit for clinical practice.

The most common mechanisms of action of anthracycline-induced cardiotoxicity is thought to be multifactorial and likely encompass the generation of reactive oxygen species and inhibition of Top2β in cardiomyocytes (7). The effects of these mechanisms are thought to be similar to other cardiac pathologies whereby diastolic dysfunction precedes the development of systolic dysfunction (25, 26, 27, 28). Furthermore, it has been shown that the use of anthracyclines agents cause an increase in isovolumetric contraction time contributing to diastolic dysfunction (26). This may explain why an increased Tei index occurred without a corresponding decrease in LVEF in a number of studies including Ergodan *et al.* where an increase in Tei index (0.41 ± 0.08) was associated with a three-fold increase in the odds of cardiomyopathy while no difference was observed for LVEF with it remaining within normal limits at a reported 61.7 ± 4.6 (21).

For the detection of anthracycline-induced cardiotoxic LVSD, current clinical practice suggests routine TTE for LVEF assessment (7). However, limitations of TTE include the requirement of high quality 2D images to ensure that subtle changes in LVEF by Simpson's biplane can be detected. Furthermore, this method is detrimentally affected by intra-observer variation, loading conditions and geometric assumptions (9). Tei index has an advantage over LVEF because high quality 2D images are not essential. In addition, Tei index is independent of loading conditions, heart rate variations and geometric assumptions (28). Further work is needed to determine the optimal 'cutoffs' for abnormal Tei index when LVEF is within normal limits for the detection of subclinical cardiotoxicity.

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Table 2 Study quality assessment using Newcastle-Ottawa Score for Cohort studies.

Study ID Reference	Definition of cardiotoxicity	Selection domain[a]	Comparability domain[b]	Outcome Domain[c]	Overall
Ayhan 2012 (14)	Not stated	***	–	**	Fair quality
Belham 2007 (15)	Mild (decrease in LVEF >10% from baseline with a final LVEF >50%) Moderate (a decrease in LVEF >10% from baseline with a final LVEF <50% and no symptoms or signs of heart failure) Severe (decrease in LVEF >10% from baseline with a final LVEF <50% and symptoms or signs of heart failure or a decrease in LVEF of any percentage leading to a final LVEF <40% irrespective of symptoms or signs of heart failure	***	*	***	Good quality
DiLisi 2011 (17)	Not stated	***	–	**	Fair quality
Dodos 2008 (1)	Absolute decline of >20% in LVEF from baseline, a decline in absolute valve >10% in LVEF from baseline to <55% or the occurrence of congestive heart failure	***	–	***	Good quality
Dogru 2013 (18)	Not stated	***	–	**	Fair quality
Elalouani 2012 (19)	Minimal: decrease in LVEF >10% but FE remains >50% Moderate: asymptomatic decrease in LVEF >10% with EF <50%. Severe: heart failure symptoms with a decrease in LVEF >10% with EF <50% or final LVEF <40%	***	–	**	Fair quality
Elbl 2006 (20)	Not stated	**	–	**	Poor quality
Erdogan 2011 (21)	Baseline LVEF decreased by ≥20% to a final value of 50% or by ≥10% to <50% and / or who exhibited clinical evidence of congestive heart failure. Based on previous studies but not ESC.	***	–	***	Good quality
Mizia-Stec 2013 (22)	Not stated	***	–	**	Fair quality
Rohde 2007 (16)	Not stated	**	–	–	Poor quality
Senju 2007 (23)	Not stated	***	–	*	Poor quality
Shaikh 2016 (24)	Clinical HF (diagnosed by Cardiologost) with a reduction in LVEF ≥5% to absolute value <55% or an asymptomatic reduction of LVEF of >0% to <55% based on Cardaci review and evaluation committee	***	–	***	Good quality
Zhang 2017 (30)	Relative reduction in LVEF ≥10% from baseline or absolute LVEF value <50% after therapy – based on ESC position paper	***	–	***	Good quality

[a]Selection domain based on: (1) representativeness of exposed cohort, (2) selection of the non-exposed cohort, (3) ascertainment of exposure, (4) demonstration that outcome of interest was not present at the start of the study, a maximum of four stars can be awarded for this domain. [b]Comparability domain based on: comparability of cohorts on the basis of the design of analysis – *control for age, **control for other factors. [c]Outcome domain based on: (1) assessment of outcome, (2) was follow-up long enough for outcomes to occur, (3) adequacy of follow-up of cohorts. A star (*) is awarded for each of the criteria meet, maximum score of 9 is attainable.
LVEF, Left ventricular ejection fraction.

The incorporation of GLS has greatly enhanced TTE's ability to detect subclinical LVSD prior to a detectable deterioration in LVEF (29). From the included studies in this review, only two studies incorporated the use of GLS (18, 24). However, neither of these directly compared Tei index and GLS in the detection of subclinical cardiotoxicity. In Dogru *et al.*, a significant deterioration in GLS post chemotherapy was only observed in the subgroup of patients with diagnosed lymphoma (GLS pre-therapy: −16.7 ± 2.8 vs GLS post-therapy: −14.6 ± 3.3,

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Table 3 Tei index evaluation and outcomes, most pertinent data highlighted in bold italics.

Study ID Reference	Timing of Tei index assessment	Tei index findings and comparison with left ventricular ejection fraction (LVEF)	Patient outcomes	Interpretation
Ayhan 2012 (14)	Mean 5 months after last cycle of chemotherapy	***Tei index at:*** ***0 months: 0.56 ± 0.11*** ***Follow-up: 0.61 ± 0.10, P = 0.001*** ***No significant change in LVEF (no data given)*** ***LVEF not compared to Tei index***	***1/45 developed symptomatic heart failure***	***Tei index increases at follow-up compared to start of chemotherapy*** ***Tei index was a more useful indicator of cardiotoxicity***
Belham 2007 (15)	1 to 3 months after completion of chemotherapy	***Tei index pre vs post: 0.41 ± 0.12 vs 0.51 ± 0.16, P < 0.0001*** ***LVEF (%) pre vs post: 63.9 ± vs 59.1 ± 7.0***	***2/51 developed severe cardiotoxicity, 2/51 moderate cardiotoxicity and 9/51 mild cardiotoxicity; no results according to Tei index***	***Tei index is useful to detect chemotherapy-induced deteriorations in left ventricular function with more statistical significance than LVEF or other echocardiographic parameter***
DiLisi 2011 (17)	0, 3 and 6 months after chemotherapy	***Tei index at:*** ***0 months: 0.36 ± 0.09*** ***3 months: 0.43 ± 0.08, P < 0.05*** ***6 months: 0.45 ± 0.08, P < 0.05*** ***LVEF (%) at:*** ***0 months: 62 ± 5*** ***3 and 6 months: 61 ± 3, P > 0.05***	Not reported	***Tei index increases at 3 and 6 months compared to start of chemotherapy treatment*** ***Tei index did not correlate with deterioration in ejection fraction***
Dodos 2008 (1)	0 months, immediately following chemotherapy, 1, 6 and 12 months	***Tei index at:*** ***0 months: 0.36 ± 0.01.*** ***Immediately post chemotherapy: 0.37 ± 0.01, P = 0.214*** ***1 month: 0.43 ± 0.01, P ≤ 0.00001*** ***6 and 12 months: states remained elevated, but no values stated (no P value)*** ***LVEF (%) at:*** ***0 months: 65.9 ± 0.6%, range 55–83*** ***Immediately following chemotherapy: significant drop in LVEF (no values given)*** ***6 and 12 months: Remained within normal limits but no values or P values given***	0/85 patients developed clinical signs or symptoms of heart failure	***Tei index increases at 1, 6 and 12 months compared to start of chemotherapy treatment. Tei index did not correlate with deterioration in ejection fraction***
Dogru 2013 (18)	0 and 1 months	***Tei index significantly increased from baseline to 1 month, P = 0.001 but no values stated***	Not reported	***Tei index increases at 1 month compared to start of chemotherapy treatment***
Elalouani 2012 (19)	0 months, during and end of chemotherapy treatment	Tei index at: ***0 months: 0.29 (0.22–0.39)*** During chemotherapy: 0.42 (0.29–0.53) ***End of chemotherapy: 0.57 (0.29–0.61)*** LVEF (%) at: ***0 months: 66% (62–73)*** During chemotherapy: 58% (50–71) ***End of chemotherapy: 51% (28–68)***	3/70 patients developed severe cardiotoxicity	***Tei index is useful indicator of cardiotoxicity***
Elbl 2006 (20)	0 and 12 months	***Tei index at:*** ***0 months: 0.45 ± 0.08*** ***12 months: 0.54 ± 0.15, P = 0.0001*** ***LVEF (%) at:*** ***0 months: 64 ± 5 (reference)*** ***12 months: 58 ± 7, P = 0.0001***	0/47 patients had clinical signs or symptoms of heart failure; 23% were reported to have an asymptomatic decline in LVEF of >10%	***Tei index increased and LVEF decreased significantly at 12 months compared to the start of the chemotherapy treatment***

(Continued)

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Table 3 Continued.

Study ID Reference	Timing of Tei index assessment	Tei index findings and comparison with left ventricular ejection fraction (LVEF)	Patient outcomes	Interpretation
Erdogan 2011 (21)	***0 and 6 months***	***Tei index for patients: Baseline: 0.43 ± 0.08 6 months: 0.47 ± 0.07, P = <0.05 Baseline LVEF (%) at: Baseline: 61.5 ± 5.1 6 months: 61.0 ± 7.2, P > 0.05***	***8/39 patients developed cardiotoxicity at follow-up (heart failure symptoms)***	***Tei index is useful indicator of cardiotoxicity Tei index is useful to detect chemotherapy-induced deteriorations in LV function with more statistical significance than EF***
Mizia-Stec 2013 (22)	***0 and 6 months***	***Tei index at: 0 month: 0.49 ± 0.09 6 months: 0.54 ± 0.1, P = 0.04 LVEF (%) at: 0 months: 63.0 ± 6.0 6 months: 63.0 ± 5.0, P > 0.05***	Not reported	***Tei index is useful to detect chemotherapy deteriorations in LV function with more statistical significance than EF***
Rohde 2007 (16)	0 months, intermediate time point and following last chemotherapy cycle.	Tei index at: 0 months: 0.42 ± 0.11 Intermediate point: 0.42 ± 0.10, $P > 0.05$ Following last chemotherapy cycle: 0.45 ± 0.1 LVEF (%) at: 0 months: 61 ± 6 Intermediate point: not stated Following last chemotherapy cycle: 56% ± 7%, $P \leq 0.001$	Not reported	Tei index not useful in the detection of chemotherapy-induced deteriorations in LV function
Senju 2007 (23)	Unclear	Tei index at: 0 months: 0.39 ± 0.17 Follow-up: 0.43 ± 0.18 (significance not stated) LVEF (%) at: 0 months: 73.4 ± 9.7 Follow-up: 72.4 ± 12 (significance not stated)	No patient developed heart failure symptoms	Tei index is not useful in the detection of chemotherapy-induced deteriorations in LV function
Shaikh 2016 (24)	0 months and 412 weeks following chemotherapy.	Tei index at: 0 months: 0.59 ± 0.14 Follow-up: 0.66 ± 0.18, $P = 0.03$ LVEF (%) at: 0 months: 64.5 ± 7.6 Follow-up: 46.9 ± 14.8, $P < 0.001$	35/80 patients developed clinically defined early cardiotoxicity and 29/85 developed heart failure; cardiotoxicity with age adjusted Δ ejection fraction OR 1.12, $P < 0.001$, Tei index OR 2.3, $P = 0.59$	Tei index not useful in the detection of chemotherapy-induced deteriorations in LV function
Zhang 2017 (30)	***0 months, after 2–4 cycles and after 6–8 cycles***	***Pulsed wave (PW) Tei index at: 0 months: 0.347 ± 0.115 2–4 cycles: 0.459 ± 0.161 6–8 cycles: 0.424 ± 0.139, P = <0.001 Tissue Doppler imaging (TDI) Tei index at: 0 months: 0.540 ± 0.107 2–4 cycles: 0.580 ± 0.986 6–8 cycles: 0.560 ± 0.140, P = 0.047 LVEF (%) on echo at: 0 months: 69.0 ± 12.4 2–4 cycles: 68.1 ± 6.6 6–8 cycles: 68.9 ± 7.5, P = 0.785***	***24/82 patients had a 10% decline in LVEF from baseline on radionuclide imaging; 5/82 patients developed LV impairment (LVEF < 50%) on radionuclide imaging***	***Tei index is useful to detect chemotherapy-induced deteriorations in LV function PW Tei index was a more reliable index that TDI Tei index***

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$P=0.004$) with no significant deterioration seen in the breast cancer subgroup (GLS pre-therapy: -16.5±6.5 vs GLS post-therapy: −16.3 ± 3.1, $P=0.82$). However, the breast cancer group did receive a lower dose of anthracyclines in comparison to the lymphoma group (168 mg/m^2 vs 346 mg/m^2) (18). Shaikh *et al* reported that in comparison to baseline GLS, there was a significant decline in post chemotherapy GLS which was observed in both the cardiotoxicity (GLS pre-therapy: −16 ± 3.6 vs GLS post-therapy: −12.6 ± 3.5, $P=0.001$) and non-cardiotoxicity groups (GLS pre-therapy −15.7 ± 4.6 vs GLS post-therapy −13.6 ± 4.1, $P=0.01$) (24).

This review has several limitations including the small sample size, which may have led to subclinical cardiotoxic event being underestimated. Indeed, there are several that did not capture any cardiotoxic events (12, 15, 16, 17, 21). Furthermore, there were challenges associated with extracting data from studies with variable methodology, lack of comparison with LVEF and/or GLS and wide ranging definitions of cardiotoxicity.

Several questions remain unanswered regarding the role of Tei index in defining and detecting subclinical cardiotoxicity. Future studies should look for better ways to define an abnormal Tei index value which is sensitive and specific in detecting subclinical anthracycline-induced cardiotoxicity. Additionally, the assessment of Tei index in comparison to the parameters currently incorporated into international guidelines including LVEF (via 2D and 3D assessment) and GLS should be sought.

Conclusion

While there is some evidence to suggest that Tei index has value in detecting cardiotoxicity, there is insufficient evidence to use it routinely. Furthermore, whether it has any advantage over assessment of ejection fraction and global longitudinal strain and how it relates to cardiotoxicity-related clinical outcomes is an area which requires further research.

Declaration of interest
The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of this review.

Funding
This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 11 March 2021
Accepted 1 April 2021
Accepted Manuscript published online 1 April 2021